II. Rejection of claims 1-6 and 8-17 under 35 U.S.C. § 103(a)

The Examiner maintained the rejection of claims 1-6 and 8-17 as unpatentable over U.S. Patent No. 5,213,811 to Frisbee et al. ("Frisbee") in view of WO 93/21921 to Haikala et al. ("Haikala"). The Examiner identified Haikala as teaching levosimendan, milrinone and pimobendan as "equivalent" drugs. Frisbee discloses compositions that may comprise milrinone. The Examiner concluded that it would have been obvious to combine the teaching of levosimendan in Haikala with the compositions disclosed in Frisbee to make the claimed invention. Applicants respectfully traverse this rejection.

The Examiner interpreted Haikala as teaching that levosimendan and milrinone are "equivalent." That interpretation does not appear to be correct. Haikala mentions at page 1, lines 21-23 that both compounds are PDE III inhibitors. Haikala does not say they are "equivalent." Haikala actually proceeds to explain some significant differences between the compounds at page 1, lines 26-27.

Levosimendan and milrinone are different in a respect that is quite relevant to the current rejection, and in particular relevant to the proposed combination of references. Milrinone is disclosed in the Frisbee patent as a drug that is highly soluble in gastric fluid and much less soluble in intestinal fluid. Frisbee at col. 1, lines 5-12 and col. 2, line 67 to col. 3, line 18. Levosimendan, on the other hand, is weakly acidic, having a pKa of about 6.3. Levosimendan is more soluble in the intestine (an environment of relatively high pH) than in the stomach (an environment of relatively lower pH). The solubility properties of the two compounds are not <u>equivalent</u>, but rather <u>opposite</u>.

The distinction drawn above between milrinone and levosimendan teaches away from the combination of references proposed by the Examiner. Frisbee's compositions are intended for drugs that are highly soluble in gastric fluid and much less soluble in intestinal fluid. Frisbee at col. 1, lines 5-12 and col. 2, line 67 to col. 3, line 1. If one skilled in the art wished to substitute another drug in place of milrinone, that person would have been motivated to choose a drug that is "highly soluble in gastric fluid and much less soluble in intestinal fluid." Levosimendan does not fit that profile. This is because, as explained above, the solubility of levosimendan is <u>directly opposite</u> that of

drugs intended for the Frisbee compositions. Any assumption of "equivalency" between levosimendan and milrinone for purposes of swapping them in the Frisbee disclosure therefore does not seem appropriate. One skilled in the art actually would have been detracted from substituting levosimendan for milrinone in the compositions of Frisbee, rather than being motivated to do so. For at least this reason, independent claims 1, 4 and 5, and all other dependent claims, should not have been obvious in view of the cited documents.

In addition to the above, all compositions in Frisbee are disclosed as providing sustained release of the drug as the composition passes through the gastrointestinal tract. For example, both the "first composition" and the "second composition" are disclosed as doing so. Frisbee at col. 2, lines 19-21 and 28-31. This property remains even though the second composition may have an initial rapid release. In columns 5-6, Frisbee provides a working example of the first and second coating. The second coating, being present in both the "first" and "second" composition, comprises Ethylcellulose and Polyvinyl Acetate Phthalate (PVAP) together with the active substance. Ethylcellulose is a water-insoluble polymer used in compositions where the complete dissolution of the formulation in the gastrointestinal tract is not desired. PVAP is an enteropolymer, i.e., it has a pH-dependent dissolution pattern. It dissolves only at a pH of 6.8 or higher. PVAP is typically used in coatings which are desired to pass the low pH conditions of the stomach intact and dissolve only at the higher pH conditions present in the small and large intestine.

The present application does not teach the use of water-insoluble polymers or enteropolymers in the compositions of the invention, as such polymers are typically used in compositions designed to release the drug over the entire gastrointestinal tract or in the lower gastrointestinal tract only. Thus, the release profile of the Frisbee compositions is contrary to the teachings of the present invention.

The Frisbee compositions also appear to favor significant formation of undesirable levosimendan metabolite (II), as levosimendan is particularly susceptible to metabolization in the large intestine. The proposed combination of references therefore does not suggest the composition of claim 1, which provides for the release of

levosimendan in a way that produces a steady-state plasma level for the levosimendan metabolite (II) of less than 20 ng/ml. The proposed combination also does not suggest the composition of claim 4, which can yield lower plasma levels of metabolite (II) than reference formulations that have slower *in vitro* dissolution rates. For at least these additional reasons, independent claims 1 and 4, and all claims depending from them, should be patentable over the cited documents.

III. Rejection of claim 7 under 35 U.S.C. § 103(a)

Claim 7 was rejected under 35 U.S.C. § 103(a) as unpatentable over Frisbee in view of Haikala and further in view of EP 0 091 767 to Yarwood et al. ("Yarwood"). Claim 7 recites that the rapid release portion of claim 5 comprises levosimendan and microcrystalline cellulose. The Examiner acknowledged that Frisbee and Haikala do not teach the use of microcrystalline cellulose as an excipient, but that it would have been obvious to use it as disclosed in Yarwood as a pharmaceutical component.

As explained above, the inventions of claims 1, 4 and 5 should be patentable over the Haikala and Frisbee disclosures. Yarwood's teaching of microcrystalline cellulose does not supply any motivation to combine those documents or any suggestion to otherwise make the inventions recited in the independent claims. All other claims in the application, including claim 7, should therefore be patentable over the cited documents as well.

If there is any fee due in connection with the filing of this Response, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: 
Steven J. Scott
Reg. No. 43,911

Date: November 3, 2003